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2019

Tolonen , H M , Airaksinen , M , Ruokoniemi , P , Hämeen-Anttila , K , Shermock , K M &
Kurki , P 2019 , ' Medication safety risks to be managed in national implementation of
automatic substitution of biological medicines : a qualitative study ' , BMJ Open , vol. 9 , no.
10 , 032892 . <https://doi.org/10.1136/bmjopen-2019-032892>

<http://hdl.handle.net/10138/310456>

<https://doi.org/10.1136/bmjopen-2019-032892>

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BMJ Open Medication safety risks to be managed in national implementation of automatic substitution of biological medicines: a qualitative study

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To cite: Tolonen HM, Airaksinen MSA, Ruokoniemi P, et al. Medication safety risks to be managed in national implementation of automatic substitution of biological medicines: a qualitative study. *BMJ Open* 2019;9:e032892. doi:10.1136/bmjopen-2019-032892

y Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-032892>).

Received 11 July 2019

Revised 06 September 2019

Accepted 24 September 2019



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ABSTRACT

Objectives To explore relevant Finnish stakeholders' perceptions on the automatic substitution of biological medicines with particular focus on medication safety and issues that need to be considered to create an appropriate model for automatic biological product substitution.

Design Qualitative interview study.

Methods Data were collected in semistructured individual (n=17), pair (n=7) and group (n=8) interviews (32 interviews, 62 participants) in 2018. Participants represented a wide range of stakeholders involved in the pharmacotherapy process: community pharmacists (n=8 interviews), authorities (n=7), prescribers (n=7), pharmaceutical industry and wholesalers (n=6), patients/customers (n=2), hospital pharmacists (n=1) and nurses (n=1). Inductive content analysis was performed.

Results Benefits of automatic substitution were identified as cost savings, more patients receiving biological treatments and enhanced continuity of treatment. Six major risk categories were identified: (1) the patient's medication is interrupted or complicated temporarily or permanently, (2) the patient uses two products with the same active substance, (3) the traceability of the product is compromised, (4) the patient cannot get into healthcare in case of problems, (5) the patient does not receive substitution-related advice from a pharmacy and (6) the patient is distracted by the support material he/she receives. Several risk mitigation measures were commonly mentioned: medication and device counselling by pharmacists (n=23), infrequent substitution interval (n=15) and better knowledge on biosimilars among healthcare providers (n=13).

Conclusion Automatic substitution of biologics is associated with risks that should be prospectively managed before implementing the procedure. The substitution also introduces new tasks and communication needs to those involved in actual medication use process, particularly to community pharmacists who will be responsible for substitution and counselling the patients.

INTRODUCTION

Biological medicines ('biologics'), especially therapeutic proteins, are used to treat an increasing number of patients over a wide range of therapeutic indications.¹ The high

Strengths and limitations of this study

- y This is the first study to explore potential medication safety risks while implementing automatic substitution of biologics.
- y Interviews are an effective method to gain an in-depth understanding of important issues when considering a model for automatic substitution of biologics.
- y A wide range of stakeholders participated in the interviews offering their viewpoints.
- y This study explored varying stakeholder views on automatic substitution of biologics rather than compared differences between the stakeholder groups.
- y The limited number of patients and nurses in the interviews may have influenced the results.

costs of original biological medicines represent a major burden on healthcare budgets.² The biosimilar concept with abbreviated approval pathway was developed in the European Union (EU) to increase competition within biologics' market.³ Subsequently, biosimilars have triggered price competition and price reductions in several countries.⁴ In Finland, hospitals have generally adopted biosimilars into their formularies mainly through their tendering processes.^{4,5} However, in ambulatory care, the uptake of biosimilars has been poor.⁶ In ambulatory care, the decision to switch between biologics is made by the prescriber and the incentives to switch from a biologic reference product to a biosimilar are weak: the social insurance reimbursement system covers the majority of expenses for the patient either way.⁵

The introduction of automatic generic substitution was an effective way to restrict the increase of medication expenditures when uptake of generic prescribing lagged.⁷⁻¹⁰ From a regulatory perspective, the approaches to demonstrate equivalence of generic small

molecule drugs and biosimilars are analogous; however, the requirements to demonstrate the similarity are more extensive for biosimilars.¹¹ This is due to the heterogeneity of the molecules produced by biotechnological processes.¹² Theoretical considerations and clinical switching studies suggest that biosimilars developed according to the EU guidance are interchangeable with their reference products.^{13–20} Furthermore, no consistent safety signals from pharmacovigilance reporting systems that monitor switching between highly similar biologics have been identified.^{12 21}

Several prominent EU regulatory agencies, including Finnish Medicines Agency, and medical societies have issued position papers supporting the interchangeability of biosimilars with their reference products under the supervision of the prescriber.²² However, since the marketing authorisation process ensures that the biosimilar has the same efficacy and safety profile as the reference product, relevant changes in treatment are not expected on switching.¹³ Thus, in countries where biosimilars have been regarded as interchangeable, the (automatic) substitution is no longer a scientific question, but a political, practical and organisational issue. The aim of this study was to explore relevant Finnish stakeholders' perceptions on the automatic substitution of biological medicines with the focus on medication safety. In the spirit of prospective risk management, our focus was to identify issues that should be considered to create an appropriate model for automatic substitution of biological medicine.

METHODS

Finnish stakeholders' perceptions on automatic substitution of biologics were explored by semistructured theme interviews. This method is particularly suitable for situations where it is desirable to elicit a wide range of views on a specific topic.²³ The theme interview is also well suited for previously unstudied topics.²⁴

Interview guide and additional interview material

The flexible interview guide with four themes was developed (online supplement material 1). The flexibility in the guide allowed a conversational and interactive approach in the interviews.²³ The themes were: (1) attitudes towards automatic substitution, (2) medication safety on substitution, (3) prerequisites for implementation and specific issues pertaining to different perspectives and (4) implementation and monitoring. The interview guide was constructed based on the study aim, and the research group's experience and knowledge that covered, for example, biosimilar policy making on the EU level, implementing the generic substitution at the national level as well as extensive medication safety research. In the interviews, a table of biosimilars that were on the market in Finland in August 2018, and a table of biosimilars authorised in the EU, but not launched in Finland were made available.

The interview guide was tested in a pilot interview. Based on the pilot, the explanations of the key terms used in the interview were added to the interview material. After this, the guide was adapted but kept open to further adjustments during the data collection, particularly regarding different stakeholder roles. The pilot interview was included in the research data.

Sampling and recruitment of the interviewees

The study sample covered a full range of national stakeholders associated with biological medication starting from the marketing authorisation to medicine distribution and patient care (online supplement material 2). The research group identified the stakeholders that were invited to participate. Purposive sampling was used to select the stakeholders to ensure the coverage of all relevant perspectives.²⁵ The following operators were included: community and hospital pharmacists, prescribers, nurses, patients/customers, pharmaceutical industry, pharmaceutical wholesalers and different authorities regarding distribution and pharmacotherapy process.

Interviewees were primary recruited through interest groups, professional associations and patient organisations. The aim of the interviews was to obtain rich and comprehensive insights from interviewees. The chosen organisations were contacted by email. The date and time for the interview were agreed by email or telephone. The invited organisations independently nominated the person or persons to participate in the interview. This influenced whether the interview was conducted as an individual, pair or group interview. Direct recruits were made in situations where it was appropriate (eg, authorities). A total of 38 interview invitations were sent.

Data collection

Written informed consent was obtained from all interviewees. The interviews were audio recorded. The interviews were conducted by HMT (female pharmacist, MSc, with training in qualitative interviews) in Finnish at places that were easily reached by the interviewees and were sufficiently private to facilitate a free and confidential exchange of information.

At the beginning of each interview, the interviewer went through the most important terms (biosimilar, substitution and medication safety) used in the interview to ensure that the concept would not cause any misunderstandings. Interviewees were encouraged to share their personal views and the possible positions of their background organisation on the topic.

Data analysis

Audio records were transcribed verbatim by a professional transcriber and transcripts were checked for accuracy by one researcher (HMT). The identities of the participants were anonymized prior to data analysis. Inductive content analysis, which is applicable for research topics which are not well-known and are expected to yield new insights,

was used.^{26 27} Data from individual, pair and group interviews were analysed in the same way, using the interview as the level of the analysis rather than analysing views of each individual participants. The data were read through several times and sentences relevant to research question were coded. Codes that had the same or similar meaning were combined. Combined codes were grouped into subcategories and further categories that formed, for example, perceived risk descriptions that were presented in a conceptual model. Suitability of the interchangeability for the biologics, as it is recognised in Finland, was not in the focus. The data were mainly analysed by one researcher (HMT). There were several sessions with the research group where data, analysis and preliminary results were discussed to improve the trustworthiness of the qualitative analysis. The most representative quotations were reported. A checklist of the consolidated criteria for reporting qualitative studies was utilised when applicable.²⁸

Ethical approval

The interviews were conducted in accordance with the Finnish National Board of Research Integrity guidelines for the ethical principles to conduct a research.²⁹ Ethical pre-evaluation was not required, as all interviewees were asked for informed consent, only adults participated in the interviews and the interviews did not cover the interviewees' personal health information.

Patient and public involvement

The patients participated in the study as representatives of their patient organisations. There was no patient or public involvement in the planning phase or design of the study. The study participants, including patient representatives, will be personally informed of the main results of the study.

RESULTS

Study participants

A total of 32 interviews with 62 participants were performed between August and November 2018 (table 1). There were 17 individual interviews. The rest were either pair (n=7) or group (n=8) interviews. Each pair and group interview included participants only from one stakeholder group. The mean duration of the interviews was 55 min (range from 30 to 98 min). All interviews were conducted face-to-face. In three interviews, there were additional participants (n=4) also via Skype or over telephone.

Most of the contacted organisations and individuals agreed to participate in the study (n=32, 84%). Six contacts did not lead to an interview. Three invited stakeholders refused to participate due to lack of knowledge or experience on the topic and two participants dropped out since a suitable interview time was not found (group interviews). No response was received for one invitation.

Table 1 Number of interviews (n=32) and background of the interviewees (n=62)

Background of the interviewees	Number of interviews (number of interviewees)
Community pharmacists	8 (15)
y National and/or local professional associations	
y Practitioners (pharmacy owners, pharmacists; MSc and BSc)	
Authorities	7 (18)
y Legislation	
y Evaluation of interchangeability of generics	
y Pricing	
y Surveillance of pharmacies	
y Reimbursement	
y Pharmacovigilance	
Prescribers	7 (7)
y Professional associations	
y Practitioners from medical specialty societies	
Pharmaceutical industry and wholesalers	6 (8)
y National interest groups	
y Pharmaceutical companies and wholesalers	
Patients/customers	2 (5)
y Patient associations	
Hospital pharmacists	1 (6)
y Hospital drug formulary management	
Nurses	1 (3)
y Specialist nurse associations	
Total	32 (62)

A summary of the characteristics of the participants is given in table 1.

General perceptions of biological medicines substitution

Practically, all participants in the interviews (n=32) preferred physician-led switching as a primary method for enhancing the use of biosimilars, whereas varied attitudes regarding automatic substitution of biologics in community pharmacies was elicited. In half of the interviews (n=16), the position of the attendees was positive to the substitution at the pharmacy level. In 25% of the interviews (n=8), interviewees suggested that there is not enough experience on biosimilars, and they saw risks that should be solved prior to initiating automatic substitution in pharmacies. Automatic substitution of biologics was deemed as a totally inappropriate model in some interviews (n=8). Some negative comments reflected distrust on quality, safety and efficacy of biosimilars in general. Positive and negative attitudes were both found among all stakeholders, including patient representatives, and all types of interviews (individual, pair or group interviews). Treatment-naïve patients were perceived to be the most suitable for substitution.

Benefits of the automatic substitution of biologics

In addition to cost-savings in healthcare (n=17), the stakeholders identified several other benefits that might

Table 2 Potential benefits of substitution at the pharmacy level as identified in the interviews (n=32)

Benefit	Description of the benefit	Citation from the interview
Savings	Society saves on drug costs (n=17)	'... that's where the big money can be saved' PRESCRIBER06
More patients can receive treatments	Lower prices can improve patients' willingness and ability to use self-injectable biological products (n=5)	'... patient's involvement in the treatment may be better if he/she gets a cheaper medicine, it is a bit of problem with expensive biological drugs before reaching annual limit for co-payment...' NURSE01
	Patients have better access to biological treatments (n=5)	'...lower prices may allow more people to receive treatment...' PATIENT04
	Patients may start biological treatment earlier (n=3)	'... maybe one should not focus only on savings here but just how you can treat patients at an earlier stage...' INDUSTRY05
	New drug treatments can be introduced without compromising sustainability of pharmacotherapy (n=2)	'... with the savings these innovative medicines can be offered to more patients...' PHARMACIST08
Continuity of treatments	Treatment can continue smoothly with another product if there is a medicine shortage (n=4)	'... if they were in a kind of generic substitution, there would be more tools for these disruptions.' PHARMACIST05
	Decreasing prices can increase the pharmacy's willingness to keep the products in stock (n=2)	'And, of course, depending on which price category the product is, if it is always available in the pharmacy as for example insulin, as soon as patient gets his medicine, he can start using it immediately.' PHARMACIST01
	Patients may receive a 3-month dose of reimbursed medication at the same time if the price of the product falls sufficiently (n=1)	'So if that price dropped so much that the customer would get it (dispensed medicine) more to take with, and on the other hand it would be a good thing for the customer not to visit pharmacy every month ...' PHARMACIST14
	Treatment can continue smoothly with another reimbursed product if there is a change in the reimbursement status of the patient's current medicine brand (n=1)	'But even in this situation (the original product is not reimbursed any more) if you speculate that there is a drug substitution and you can switch directly to the biosimilar, so this recipe 'exchange rally' is much smaller.' PHARMACIST01
	Automatic substitution could improve immediate availability if pharmacies were aware of the product that has to be dispensed (n=1)	'...for example, in this Neupogen case, you should keep four different products in stock when you don't know what the doctor prescribes, but with the substitution you only need one product to start the treatment...' AUTHORITY18

be achieved with implementing biologics' substitution (table 2). More patients can receive treatments, if savings result in increased number of patients on biological treatment (n=5), initiation of biological treatment in earlier phase (n=3) or introduction of novel treatments for new patients (n=2). Substantial price reductions may also increase patients' willingness and ability to use biologics (n=5), if the price reductions are substantial. Continuity of treatment was also identified as a potential benefit, for example, in the case of medicine shortages (n=4).

The perceived medication safety risks and their management

Most of the risks with biologics' substitution identified in the interviews were related to the interruption or complication of patient's pharmacotherapy because of issues such as inadequate knowledge of the administration device (n=19), medicine availability problems (n=12) or patient's distrust to the biosimilar medicine itself (n=11) (table 3). For example, differences in packages and complex naming (n=11) can introduce a risk for duplicate therapy. Traceability of the dispensed product

name and batch number (due to long-term side effects; n=8, or unavailability of the dispensed product name or batch number; n=5) and insufficient availability of healthcare contacts (n=12) were also identified as medication safety risks in substitution in several comments. Lack of appropriate training for patients in the pharmacy and the inconsistencies between the pharmaceutical product-specific patient information materials were mentioned as risks in some interviews.

Several methods to minimise medication safety risks were proposed in the interviews. Medication and device counselling provided by pharmacists (n=23), infrequent substitution interval (n=15) and better knowledge on biosimilars among healthcare providers (n=13) were identified as potential remedies in multiple interviews.

Substitution frequency

The interviewees were asked about optimal substitution interval for biologics. Only three interviewees agreed that the current generic substitution interval of 3 months (eg, how often the medicine could be substituted in the

Table 3 Perceived medication safety risks and their management measures as identified in the interviews (n=32)*

Potential risk	Descriptions of perceived risks with manifestation	Methods to minimise risk as identified in the interviews (n=32)
The patient's medication is interrupted or complicated temporarily or permanently	The patient does not know how or is unable to use the administration device correctly (n=19)	y Pharmacy provides medication counselling including device counselling with optional injection training (n=23)
	y The patient feels that the new administration device is difficult to use	y The interval† between substitutions should be longer for biological drugs than for generic medicines (n=15)
	y Patient fails to administer medicine or he/she is not able to repeat administration	y Further training of healthcare professionals on biosimilars (n=13)
	y New administration device is not suitable for the patient (handicap, visual impairment)	y Consistent, positive attitude towards substitution across healthcare and pharmacies (n=9)
	y Too wide a range of different devices is available	y A motivating conversation with the patient by a doctor and nurse (n=8)
	The medicine is not available at the right time (n=12)	y Ensuring at every pharmacy and healthcare visit that the patient can use the device correctly (n=8)
	y The pharmacy does not have the product in stock	y Medication monitoring (n=8)
	y There is a medicine shortage	y The patient knows where to contact in case of problems (n=7)
	The patient does not trust the new medicine (n=11)	y Prescriber can prohibit substitution if necessary (n=7)
	y The patient has benefited significantly from the original product and does not want to change	y Evaluation of the interchangeability of devices in a regulatory process (n=6)
	y The patient receives conflicting messages from different healthcare professionals	y Dispensing of biologics based on an appointment or pre-order (n=6)
	y The substitution will surprise the patient at the pharmacy	y Switches and substitution are avoided if medication has not been stabilised (n=6)
	y Patient is suspicious due to different product appearance and trade names	y Evaluation of biological medicines suitable for substitution by the regulatory authority (n=6)
	The patient experiences adverse reactions after substitution (n=11)	y Postmarketing surveillance of medicines (n=5)
	y Reactions to excipients	y Regional co-ordination/co-operation between healthcare and pharmacies (n=4)
	y Nocebo-effect	y Substitution policy prevents shortages by supporting pharmaceutical companies to anticipate the market (n=3)
	y Large-scale substitution may reveal problems that were not previously detected	y Mandatory reserve supplies of biological medicines (n=2)
	Concern about losing the medicine's effectiveness (n=8)	y Providing reliable drug information sources for the patient (n=2)
	y The development of drug antibodies is accelerated by repetitive switches	
	y There is no large-scale experience on repetitive switches	
The patient uses two products with the same active substance	Based on the appearance or name of the product, it is not possible to determine whether the active substance is the same (n=11)	y Demonstrating administration devices in drug counselling (visually) (n=9)
	y Different appearance of packages	y Prescriber can prohibit substitution (n=7)
	y Different trade names	y Printing drug lists and checking medication (n=1)
	y Generic names can be confusing	y The new product is marked with a label that indicates the substitution (n=1)
	y Patient recognises only the established brand name	y The new product is not delivered too early, so the patient does not have two products at the same time at home (n=1)
	The patient does not understand that substitution has taken place (n=8)	y Pharmacist invalidates the previous prescription when substituting (n=1)
	y Patients with polypharmacy, the elderly, patients with impaired cognition	
The traceability of the product is compromised	The patient has two prescriptions for the same active substance (n=3)	
	y The patient has a prescription for the original product and another prescription for the biosimilar	
	The biological drug can have long-term side effects (n=8)	y The interval between substitutions should be longer for biologics than for generic medicines (n=15)
	y The product that caused a side effect cannot be traced	y Promoting two-way information sharing between pharmacy and healthcare services (n=10)
	In case of a side effect, the product cannot be traced (n=5)	y Switches and substitution are avoided if medication has not stabilised (n=6)
	y The physician is not aware of what brand and what batch the patient has used	y Introduction of a drug certification system (automatic registration of the dispensed package and batch) (n=6)
	y Patient refers only to the originator's brand name	y Development of information systems so that the batch number of the delivered product is also registered in the electronic prescription centre (n=4)
		y Prescriber can check the brand name of the supplied medicine at the electronic prescription centre (n=3)

Continued

Table 3 Continued

Potential risk	Descriptions of perceived risks with manifestation	Methods to minimise risk as identified in the interviews (n=32)
The patient cannot get into healthcare in case of problems	Healthcare is overloaded due to substitution (n=12) y Substitution increases patient contact with healthcare y Patients with substituted medicine would be in closer follow-up. The patient contacts the physician to obtain a substitution refusal	y Further training of healthcare professionals on biosimilars (n=13) y Consistent, positive attitude towards substitution across healthcare and various pharmacies (n=9) y A motivating conversation with the patient by a doctor and nurse (n=8)
The patient does not receive substitution-related advice from a pharmacy	On behalf of the patient customers (n=5) y For example, a relative can apply for a medicine on behalf of a patient New methods to dispense medicines (n=1) y The patient can apply for a medicine from the 'smart box' when convenient	y Medication counselling with both visual and written material (n=7) y Prescriber can prohibit substitution (n=7)
The patient is distracted by the support material he receives	There may be differences in written material received by the patient (n=2) y Material for various products is accumulated The availability of additional materials may vary by product (n=2) y Pharmaceutical company supplies additional product-specific material such as web pages, storage and shipping boxes	y Generic and harmonised risk minimisation materials (n=2)

*Please note, 'patient perspective' can be either patient representative's view or other stakeholder representative's assumption on patient's view.

†In Finland, the substitution interval for generic small molecules (generic substitution interval), eg, how often patient's medicine could be substituted at the pharmacy, is related to the reference price that establish the reimbursement level and is confirmed quarterly (reference price interval) (The Social Insurance Institution of Finland. Generic substitution and the reference price system. Available: <https://www.kela.fi/web/en/medicine-expenses-generic-substitution-and-the-reference-price-system>(accessed June 2019)).

pharmacy⁵) would be suitable for biologics and none recommended to have an interval of 1 month. The most popular interval for substitution was 12–24 months (n=13). In some interviews, the participants did not want to mention any precise frequency but mentioned that it 'should be done rarely'. Both the validity period of a prescription and the adjusted reference price intervals for biologics were suggested to determine the interval of biologics' substitution.

Participants suggested an association between substitution frequency and medication safety and pharmaceutical market attractiveness (table 4). It was suggested that a

long substitution interval may increase medication safety compared with shorter intervals. On the contrary, pharmaceutical companies' interest to enter local pharmaceutical market may be compromised if the substitution interval is too long.

Tasks and responsibilities of the patients and healthcare professionals

Automatic substitution was predicted to bring new tasks to community pharmacists (figure 1). Lack of information sharing between community pharmacists and nurses who are involved in patient counselling was noted in

Table 4 Influence of the substitution frequency on medication safety and attractiveness of the pharmaceutical market in Finland emphasised in the stakeholders' interviews (n=32)

	Short substitution interval	Long substitution interval
Medication safety	Positive impact on y Continuation of treatment in case of shortages of a particular product Negative impact on y Device expertise of the patient y Traceability of the product and batch number y Management of support material for the patient y Concerns on immunogenicity	Positive impact on y Device expertise of the patient y Traceability of the product and batch number y Management of additional patient material Negative impact on y Continuity of treatment in case of shortages
Attractiveness of pharmaceutical market	Negative impact on y Predictability of pharmaceutical market y Stock management in pharmacies Uncertain impact on y Competition between products	Positive impact on y Predictability of pharmaceutical market y Stock management in pharmacies Negative impact on y Competition between products (prevents rapid reaction to price changes)

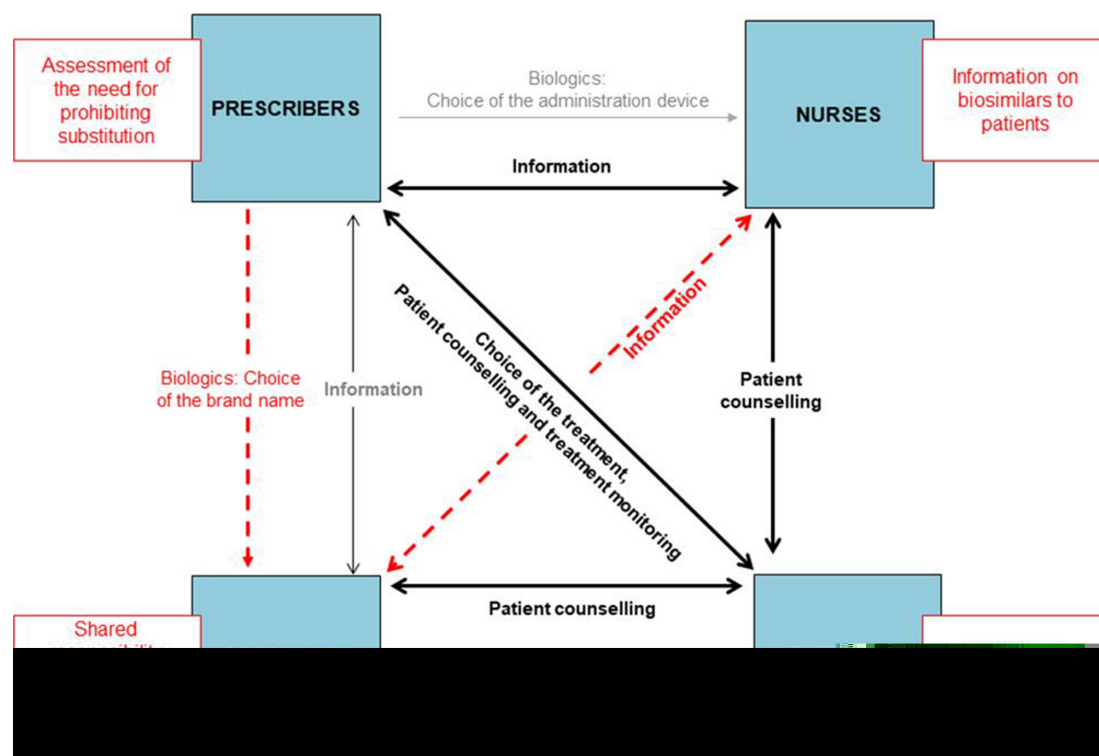


Figure 1 Existing interactions (black lines) between patients and healthcare professionals in biological medicine treatment in Finland and new tasks (red boxes) and new interactions (red dashed lines) between patients and healthcare professionals induced by automated substitution of biologics identified in the stakeholders' interviews (n=32).

several interviews. It was highlighted by interviewees that this information pathway should be developed for effective and consistent counselling on administration devices for patients. Multiple interviewees stated that collaboration between teams in healthcare and pharmacies should be improved before introducing automatic substitution of biologics. On the contrary, patients' role as a partner was discussed by the various interviewees.

DISCUSSION

The stakeholders had a generally positive attitude to the biologics' substitution at the pharmacy level. Treatment-naïve patients were regarded as the most suitable targets for substitution. The stakeholders identified several benefits and risks related to automatic substitution of biologics. Many of the risks that were identified in the interviews are applicable also to generic substitution, such as patients' expected distrust towards a new medicine and a parallel use of the same active ingredients in different products (table 3). Traceability of the dispensed product name and batch number, and patients' knowledge and training for a new administration device were identified as risks that are not shared with generic substitution. On the contrary, multiple mitigation measures against medication safety hazards were also identified, such as infrequent substitution interval, improved knowledge of biosimilars among healthcare personnel and administration device counselling at pharmacies. These measures can allocate some new tasks to community pharmacists.

Education of healthcare providers and patient counselling

Our study indicates that the personnel in healthcare units and community pharmacies need substantial detailed information on biosimilars, which is consistent to previous findings.^{30–32} The outcome of automatic substitution may be negatively influenced if the provided information is ambiguous or not sufficiently detailed.³³ The attitudes of the prescriber or other providers towards substitution have been shown to have an impact on the patient's acceptance to switch medicine and the perceived outcome of the switch.^{34–35} In generic substitution, lack of appropriate information has been shown to be confusing and raise doubts regarding the quality, safety and efficacy of the generic product.^{36–38}

Regarding the experience of generic substitution, it is important to provide consistent information to patients about biosimilars, the reasons for the switch and the product in question. Based on the assessment by the regulatory authorities, the marketing authorisation holder may be required to produce risk minimisation material, such as patient 'alert cards' used to manage the adequate monitoring of treatment.³⁹ In general, the risk minimisation material of biosimilars should be consistent with the information of the reference product. In order to avoid confusion among patients, these materials should be as harmonised as possible.³⁹

Our study identified potentially new roles for community pharmacists to facilitate safe and effective substitution of biologics. In Finland, the patient counselling on

